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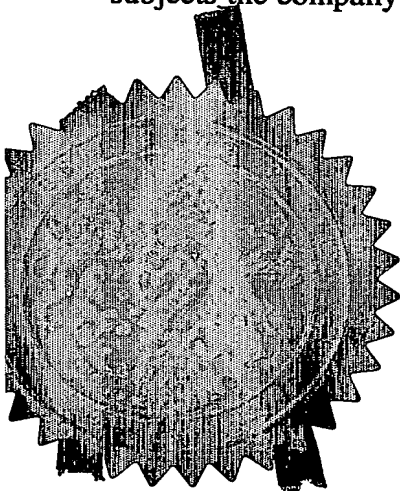
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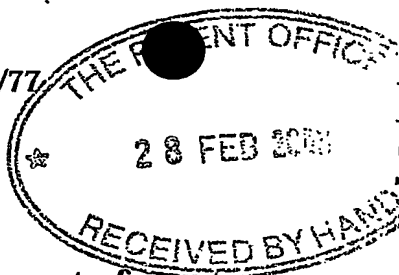
Stephen Hordley

Dated

29 July 2003

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Patents Form 1/77

Patents Act 1977
(Rule 16)The
Patent
Office03MAR03 E760791-9 002890
P01/7700 0100-0304648.9

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference

REP06758GB

2. Patent application number

(The Patent Office will fill in this part)

0304648.9

28 FEB 2008

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)Arachnova Therapeutics Ltd
95 Halkett Place
St. Helier
Jersey
JE1 1BX
CHANNEL ISLANDSPatents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

8137770001

4. Title of the invention

NEW THERAPEUTIC USE OF
4-(2-FLUOROPHENYL)-6-METHYL-2-(1-
PIPERZINYL) THIENO [2,3-D] PYRIMIDINE5. Name of your agent (*if you have one*)

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)Broadgate House
7 Eldon Street
London
EC2M 7LHPatents ADP number (*if you know it*)

745002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (*if you know it*) the or each application number

Country

Priority application number
(*if you know it*)Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer 'Yes' if:*

YES

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 3

Claim(s) 1

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

NO

11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date

28 February 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

R E Perry

020 7377 1377

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Notes

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NEW THERAPEUTIC USE OF 4-(2-FLUOROPHENYL)-6-METHYL-2-
(1-PIPERAZINYL)THIENO[2,3-D]PYRIMIDINE

Field of the Invention

This invention relates to a new use for a known compound.

5 Background of the Invention

4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine monohydrate hydrochloride is known (see US-A-4695568) and has shown activity as an antidepressant. It has serotonin and noradrenergic reuptake blocking properties and this is thought to be the mechanism for its action as an antidepressant. The compound
10 also has 5HT-3 blocking activity.

Functional bowel disorders are very common and include irritable bowel syndrome (IBS) and functional dyspepsia. IBS is the most common disorder diagnosed by gastroenterologists and one of the more common encountered in general practice. The overall prevalence rate is similar (approx 10%) in most industrialised countries.
15 Some estimates of prevalence have reached 20%. The illness has a large economic impact on health care use and indirect costs, chiefly through absenteeism.

IBS falls into two categories of equal prevalence, constipation-predominant and diarrhoea-predominant. The available treatments are generally poor.

A recent approach to treating diarrhoea-predominant IBS has involved the use
20 of alosetron. This drug works by blocking the 5HT-3 receptor. Other drugs with this mechanism of action have shown some limited activity in this disease, including ganisetron. Alosetron, although effective, was withdrawn due to side-effects on the colon.

A recent approach to treating constipation-predominant IBS involved agonising
25 the 5HT4 receptor. Two such agonists are in clinical trials, i.e. tegaserod and prucalopride. Other approaches being explored include using 5HT1 agonists such as buspirone.

Functional dyspepsia is characterised by impaired accommodation of the stomach to a meal and epigastric pain discomfort or pain. There is often early satiety
30 and weight loss. The disorder is not well understood. Treatments include antispasmodics and drugs affecting gut motility. Early studies suggest that buspirone and serotonin reuptake inhibitors may be useful.

Summary of the Invention

Surprisingly, it has been found that the known compound identified above
35 (referred to herein as MCI-225) has activity in the treatment of functional bowel

disorders. Its combination of serotonin and noradrenergic reuptake blockade and 5HT-3 receptor blockade has not previously been clearly identified as being responsible for activity in functional bowel disorders. Furthermore MCI-225, at doses effective in the treatment of bowel disorders, can produce a lower incidence of some of the side-effects which are commonly known to be associated with the clinical use of selective serotonin reuptake inhibitors, for example the production of nausea and vomiting or the induction of sexual dysfunction. It will be appreciated that any suitable form of the active principle may be used, e.g. another salt form, or a prodrug or active metabolite.

Description of Preferred Embodiments

10 By means of this invention, functional bowel disorders can be treated, e.g. controlled or prevented. For this purpose, the active compound can be formulated in any suitable manner together with a conventional diluent or carrier. The active compound is preferably administered by the oral route; other suitable routes of administration include sublingual/buccal, transdermal, intramuscular, intranasal, rectal, 15 parenteral, subcutaneous, pulmonary and topical. An effective dose of the active agent will depend on the nature and degree of the complaint, the age and condition of the patient and other factors known to those skilled in the art. A typical daily dosage may be 0.1 mg to 1 g.

A pharmaceutical composition containing the active ingredient may be in the 20 form of a sublingual tablet or patch. Suitable compositions for oral use include tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups and elixirs. Suitable additives include sweetening agents, flavouring agents, colouring agents and preserving agents. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable 25 excipients, e.g. inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay 30 disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated, to form osmotic therapeutic tablets for controlled release. Hard gelatin capsules may include an inert solid diluent, for example calcium carbonate, calcium

phosphate or kaolin; soft gelatin capsules may include water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

The data on which this invention is based will now be described. In a study using intact animals, the ability of a drug to inhibit the reflex depressor response to colorectal distension can be assessed. In this model, an inhibition of the reflex indicates modulation of visceral nociceptive neurotransmission and, therefore, the use of the drug in functional bowel disease (e.g. IBS); see Kozłowski *et al* 2000, Gut 46, 474-480. Allodynia and visceral pain are important components of functional bowel disease.

10 Study

Experiments were performed on male Sprague-Dawley rats (250-300g). Anaesthesia was induced with isoflurane (2.5% in oxygen) and maintained with alpha chloralose (80 mg/kg i.v.). The left carotid artery was cannulated for the measurement of blood pressure and heart rate and the left jugular vein cannulated for drug administration. A tracheal cannula was implanted for artificial respiration if required. A 1cm long latex balloon was inserted intrarectally so that the tip of the balloon was 2 cm from the anal verge (Kozłowski *et al*, 2000, Gut 46, 474-480). The balloon was connected via a double lumen cannula to a pressure transducer and also to a saline filled syringe for inflation/deflation of the balloon. Throughout the experiment body temperature was kept constant at 36-38 C using a homeothermic blanket.

Once stable baseline parameters were obtained (approximately after 20 minutes) the balloon was rapidly inflated with increasing volumes of saline (0.5-2.5 ml) for 30 seconds at 5 minute intervals and the resultant change in blood pressure recorded. Three distinct response curves were constructed with a 10 minute stabilisation period between each curve. In one group of animals, 10 minutes prior to the commencement of the final distension response curve, a single bolus of MCI-225 (3 mg/kg) was administered intravenously; in a second group of animals, a single bolus dose of vehicle was administered. The effect of MCI-225 and vehicle was determined by analysing the changes in colorectal distension that evoked depressor response.

CLAIMS

1. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperaziny)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of a functional bowel disorder.
- 5 2. Use according to claim 1, wherein the salt is the hydrochloride monohydrate.
3. Use according to claim 1 or claim 2, wherein the disorder is irritable bowel syndrome.